

# 4-O-Methylhonokiol: A lesser-known neolignan from *Magnolia* species with diverse and promising pharmacological properties

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## ABSTRACT

This is the first review of 4-O-methylhonokiol (MH) from *Magnolia* species, a lesser-known neolignan. Contents of the review include an introduction to neolignans, the botany of selected *Magnolia* species, and the chemistry and plant sources of MH, followed by a brief description of the pharmacokinetics and metabolism of MH in rats. Pharmacological properties of MH include anticancer properties, antidiabetes properties, anti-inflammatory effects, attenuation of memory impairment, anxiolytic or antianxiety effects, antiobesity effects, hair growth promotion, and inhibition of embryo anomalies. Other pharmacological properties of MH include antiseizure, neuroprotective, peroxisome proliferator-activated receptor modulation, inhibition of osteoclastogenesis, protection against liver injury, treatment of cannabis dependence, alleviation of blood-brain barrier dysfunction, cognitive dysfunction amelioration, and cannabinoid receptor inverse agonist. Wherever possible, the properties of MH and its derivatives are compared with those of well-known neolignans such as honokiol and magnolol. Some future research and prospects are suggested.

## INTRODUCTION

Neolignans are secondary plant metabolites that are oxidative products of phenylpropanoids, a large family of organic compounds synthesized by plants from amino acids such as phenylalanine and tyrosine (Zálezák *et al.*, 2019). They are phenolic compounds with dimeric structures linking two units via a C–C or C–O linkage. Neolignans with C–O linkages are sometimes referred to as oxoneolignans (Teponno *et al.*, 2016). Among *Magnolia* species, well-reviewed neolignans are honokiol (Ong *et al.*, 2020; Rauf *et al.*, 2018) and magnolol (Chen *et al.*, 2011; Lin *et al.*, 2021). Neolignans possess biological activities such as anticancer, estrogenic, antiviral, antimicrobial, neuroprotective, antihypersensitive, and antioxidant properties. Other classes of compounds isolated from *Magnolia* species are

flavonoids, phenylpropanoids, coumarins, alkaloids, terpenoids, and lignans (Lee *et al.*, 2011a).

Most of the studies on the pharmacological properties of neolignans from *Magnolia* are from three species. The species are described below.

*Magnolia officinalis* Rehder & E. Wilson is native to China, occurring at altitudes of 300–1,500 m (Xia *et al.*, 2008; TSO, 2021). The species is a deciduous tree that reaches 20 m in height and produces a thick, brown, but not fissured bark. Young shoots are downy and yellowish grey. Leaves are obovate, rounded at the apex, pale green above, and downy beneath. Flowers are white, fragrant, and cup-shaped (Fig. 1). Fruits are elongated with a rounded tip. In China, the dried bark of *M. officinalis* (Houpo) is an important medicinal herb having a wide range of biological and pharmacological properties (Luo *et al.*, 2019).

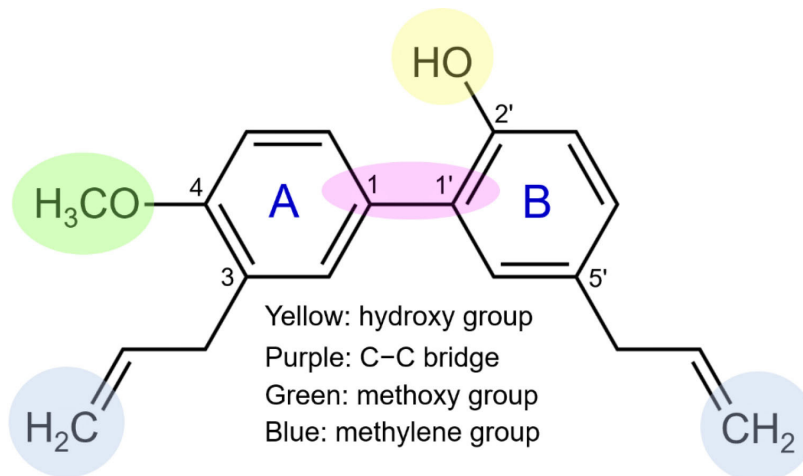
*Magnolia obovata* Thunb. is a deciduous tree species that is native to the deciduous broad-leaved temperate forests of Hokkaido in Japan (Kikuzawa and Mizui, 1990). The species is cultivated in China (Xia *et al.*, 2008) and has naturalized in Korea (Kwon and Oh, 2015). In Japan, *M. obovata* is a beautiful tree that reaches 20 m in height (TSO, 2021). Its bark is thick, brown, and not fissured. Leaves are large, leathery, obovate, green above,

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**Figure 1.** Flowers of *M. officinalis* (left), *M. obovata* (middle), and *M. grandiflora* (right).



**Figure 2.** The chemical structure of 4-O-methylhonokiol.

and bluish-white beneath. Flowers are large, strongly fragrant, and cup-shaped, and they produce petals that are creamy white with purplish-red filaments and yellow anthers (Fig. 1). Fruits are red and cone-shaped with a tapering tip.

*Magnolia grandiflora* L. is a medium to large evergreen tree that is native to North America, up to 30 m in height with a dense pyramidal crown (Lim, 2014). The bark is greyish brown, scaly, and fissured. Leaves are leathery, broadly ovate, dark green above, and yellowish brown with tomentose beneath. Flowers are large, showy, fragrant, and white (Fig. 1). Fruits are cylindrical to ovoid with greyish-yellow tomentose. They contain seeds that are ovoid, glossy, and bright red.

#### 4-O-METHYLHONOKIOL

MH (3,5'-diallyl-2'-hydroxy-4-methoxybiphenyl) is a neolignan with the molecular formula of  $C_{19}H_{20}O_2$  and molecular weight of 280 g/mol (Lee *et al.*, 2011a). Its IUPAC name is 2-(4-methoxy-3-prop-2-enylphenyl)-4-prop-2-enylphenol. Structurally, MH has a biphenyl skeleton linked by a C–C bridge at C1 and C1' (Fig. 2). There is a methylene ( $-CH_2$ ) group at C3 and at C5' (diallyl moiety), a methoxy ( $-OCH_3$ ) group at C4 of the A ring, and a hydroxy ( $-OH$ ) group at C2' of the B ring. MH has a chemical structure that is similar to that of honokiol (3,5'-diallyl-4,2'-dihydroxybiphenyl) which has a  $-OH$  group at C4, instead of a  $-OCH_3$  group. Both MH and honokiol have a  $-OH$  group at C2'.

MH has been isolated and identified from *Magnolia* species. They include *M. officinalis* (Luo *et al.*, 2019; Poivre and Duez, 2017), *M. obovata* (Chan *et al.*, 2021; Min, 2008),

*M. grandiflora* (Clark *et al.*, 1981; Schühly *et al.*, 2007), *M. virginiana* (Chandra and Nair, 1995; Nitao *et al.*, 1991), and *M. garrettii* (Schuehly *et al.*, 2010). MH was first reported in the seeds of *M. grandiflora* by El-Ferally and Li (1978). In the seeds of *M. grandiflora* (Fig. 3), MH (~10%) was found to be the major neolignan, followed by magnolol (1%–2%) and honokiol (1%–2%) (Schühly *et al.*, 2009b). From 20 kg of *M. obovata* stem bark, 8.5 g of MH was obtained (Singha *et al.*, 2019). In *M. officinalis* bark (Fig. 3), the content of MH was 16.6% with 16.5% of honokiol and 12.9% of magnolol (Lee *et al.*, 2009a).

The pharmacokinetics of MH was first studied in rabbit plasma using an oral dose of 0.6 mg/kg (Li *et al.*, 2011). Results showed that MH was absorbed at 0.85 hours and had a short half-life of 0.35 hours. A more recent study investigated the pharmacokinetics and metabolism of MH in rats (Yu *et al.*, 2014). As a drug candidate, MH possessed a pharmacokinetic profile characterized by poor oral absorption and high systemic clearance. These results suggest that the pharmacokinetic properties of MH can be optimized by synthesizing analogs with improved metabolic stability.

#### PHARMACOLOGICAL PROPERTIES

##### Anticancer

When tested against HeLa cervical, A549 lung, and HCT116 colon cancer cells, MH from the stem bark of *M. obovata* was reported to be cytotoxic with  $IC_{50}$  values of 12.4, 14.1, and 14.4  $\mu$ g/ml, respectively (Youn *et al.*, 2008). In comparison,



**Figure 3.** Seeds of *M. grandiflora* (left) and bark of *M. officinalis* (right).

honokiol and magnolol displayed stronger cytotoxicities, 7.7–8.6 and 11.1–11.4  $\mu\text{g/ml}$ , respectively.

Among the three key bioactive compounds of the *M. officinalis* bark, MH, honokiol, and magnolol showed antiproliferative activities in SCC-9 and Cal-27 oral squamous cancer cells (Bui *et al.*, 2020). Against SCC-9 cancer cells, MH (5.2  $\mu\text{g/ml}$ ) and honokiol (5.5  $\mu\text{g/ml}$ ) had significantly stronger cytotoxicity than magnolol (7.8  $\mu\text{g/ml}$ ), based on  $\text{IC}_{50}$  values and a 72 h treatment period. Against Cal-27 cells, cytotoxicities of all three compounds were comparable with  $\text{IC}_{50}$  values of 5.6, 6.6, and 5.1  $\mu\text{g/ml}$ , respectively. Related *in vivo* studies showed that MH suppressed oral tumors in mice more effectively than honokiol and magnolol did (Zhang *et al.*, 2020). While these three neolignans displayed efficacy in inhibiting oral cancer cells, their anticancer effects were enhanced when combined as in natural extracts (Zhang *et al.*, 2020).

MH inhibited colon cancer cell growth of SW620 and HCT116 (Oh *et al.*, 2012) and prostate cancer cells of PC-3 and LNCap (Lee *et al.*, 2013) via apoptotic cell death, p21-mediated suppression of nuclear factor (NF)- $\kappa\text{B}$  activity, and cell cycle arrest. MH inhibited cell growth and induced apoptosis in HN22 and HSC4 oral squamous cancer cells and in xenograft tumors (Cho *et al.*, 2015). Significant apoptotic effects were observed following MH treatment of 20–40  $\mu\text{M}$  for both types of cancer cells. MH inhibited the growth of SiHa human cervical cancer cells by triggering the intrinsic apoptosis pathway and inhibiting the PI3K/Akt survival pathway (Hyun *et al.*, 2015). MH induced cytotoxicity against PE/CA-PJ41 oral squamous cancer cells with an  $\text{IC}_{50}$  value of 1.25  $\mu\text{M}$  (Xiao *et al.*, 2017). The antitumor activity was mediated via reactive oxygen species (ROS) generation, mitochondrial membrane potential disruption, and cell cycle arrest, including the modulation of Bcl-2/Bax proteins.

Overall, MH exerts anticancer properties via molecular mechanisms of nuclear factor  $\kappa\text{B}$  (NF- $\kappa\text{B}$ ) suppression (Oh *et al.*, 2012), activation of PPAR $\gamma$  (Lee *et al.*, 2013), induction of ROS (Xiao *et al.*, 2017), disruption of mitochondrial membrane potential (Xiao *et al.*, 2017), the PI3K/Akt survival pathway inhibition (Hyun *et al.*, 2015), modulation of Bcl-2/Bax proteins (Xiao *et al.*, 2017), and induction of p21 protein expression (Oh *et al.*, 2012). A study by Han and Van Anh (2012) showed that MH downregulated P-glycoprotein expression and could serve as an effective agent for reducing the multidrug resistance of cancer cells.

### Anti-inflammatory

The results of *in vitro* and *in vivo* experiments showed that MH possessed anti-inflammatory properties by inhibiting NF- $\kappa\text{B}$  (Oh *et al.*, 2009). The neolignan inhibited nitric oxide (NO) generation in RAW 264.7 macrophage cells with an  $\text{IC}_{50}$  value of 9.8  $\mu\text{M}$ . When topically applied, MH inhibited ear edema inflammation in rats. Similar tests conducted earlier also showed the anti-inflammatory activity of MH (Zhou *et al.*, 2008). The anti-inflammatory activity of MH involved the inhibition of inducible nitric oxide synthase (iNOS) and cyclooxygenase-(COX)-2 expression by downregulating signaling pathways of c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) and inactivation of NF- $\kappa\text{B}$ .

The anti-inflammatory activity of MH was accompanied by COX-2 inhibition with an  $\text{IC}_{50}$  value of 1.5  $\mu\text{g/ml}$  (Schühly *et al.*, 2007). Compared to its derivatives, MH displayed the strongest inhibition of 95% for COX-2 and 96% for leukotriene B4 (Schühly *et al.*, 2009a). From the seeds of *M. grandiflora*, the strongest inhibition was displayed by MH (1.2  $\mu\text{g/ml}$ ) compared to honokiol (1.7  $\mu\text{g/ml}$ ) and magnolol (2.0  $\mu\text{g/ml}$ ) (Schühly *et al.*, 2009b). MH strongly inhibited COX-2 activity ( $\text{IC}_{50}$  value of 0.06  $\mu\text{M}$ ) and prostaglandin production mediated by COX-2 ( $\text{IC}_{50}$  value of 0.10  $\mu\text{M}$ ) in zymosan-injected mice (Kim *et al.*, 2015).

Derivatives of MH also possess anti-inflammatory properties in a lipopolysaccharide- (LPS-) induced neuroinflammation mouse model (Sivak *et al.*, 2019). The anti-inflammatory effect of a novel derivative of MH in the brains of rats with LPS-induced neuroinflammation was four times that of control rats (Kiseleva *et al.*, 2020). Recently, an assessment of novel structural honokiol analogs with a 4'-*O*-(2-fluoroethyl) moiety showed potent anti-inflammatory activity (Vaulina *et al.*, 2021). The anti-inflammatory activity of MH involved the inhibition of COX-2 (Chicca *et al.*, 2015) and cannabinoid receptor type 2 (Gertsch and Anavi-Goffer, 2012).

### Attenuation of memory impairment

A group of scientists from the Chungbuk National University in Korea studied MH and its effects on memory impairment in mice. The following are some of the results in chronological order:

1. MH attenuated scopolamine-induced memory impairment function in mice by inhibiting acetylcholinesterase activity ( $\text{IC}_{50}$  value of 12 nM)

- (Lee *et al.*, 2009a). This value was more than 11 times stronger than that of tacrine, used as a positive control.
- MH suppressed beta-amyloid (A $\beta$ )-induced memory impairment in male ICR mice via the inhibition of neuronal cell death and ROS generation (Lee *et al.*, 2010).
  - Memory impairment in an Alzheimer's disease (AD) mouse model was attenuated by MH through modulation of oxidative damage of enzymes by reducing A $\beta$  generation and accumulation (Choi *et al.*, 2011).
  - MH attenuated memory impairment in presenilin 2 mutant mice through the reduction of oxidative damage, inactivation of astrocytes, and suppression of the ERK pathway (Lee *et al.*, 2011b).
  - $\beta$ -Amyloid-induced memory impairment in mice was attenuated by MH via reduction of oxidative damage and inactivation of the p38 MAP kinase pathway (Lee *et al.*, 2011c).
  - MH ameliorated LPS-induced memory deficiencies and checked neuroinflammation (Lee *et al.*, 2012a).
  - MH ameliorated memory impairment in a transgenic mice model of AD by downregulating secretase activity and inhibiting oxidative stress and neuroinflammatory responses (Lee *et al.*, 2012b).

#### Anxiolytic effect

Anxiety disorders are common among adults and adolescents, and anxiolytic or antianxiety drugs are in great demand and are prescribed to manage such mental disorders. Interestingly, MH has been found to possess such psychopharmacological properties. A study reported that, after 7 d of treatment, MH exerted anxiolytic-like effects on male ICR mice, and the process might be mediated by the transmission of  $\gamma$ -aminobutyric acid (GABA) followed by an increase in chloride channel opening (Han *et al.*, 2011). Another study reported that MH at 3  $\mu$ M potentiated GABA<sub>A</sub> receptors 20 times stronger than honokiol, both at the same concentration (Baur *et al.*, 2014). This affirms the potential of MH to be developed into an anxiolytic agent.

#### Antidiabetes

Diabetic nephropathy and diabetic cardiomyopathy are long-term disorders of type 2 diabetes. A study on the effect of treatment with MH for three months on diabetic nephropathy progression in a type 2 diabetes murine model showed that MH prevented renal oxidative stress and inflammation (Ma *et al.*, 2019). The protection might be attributed to oxidative stress attenuation and lipid metabolic improvement. Results of another study revealed that MH protected male C57BL/6J mice against diabetic cardiomyopathy by activation of AMP-activated protein kinase (AMPK) and improvement in cardiac lipid metabolism (Zheng *et al.*, 2019).

#### Antiobesity

MH protected against high-fat diet-induced obesity and systemic insulin resistance in male C57BL/6J mice (Zhang *et al.*, 2014a). Lipid accumulation and inflammation in adipose tissue, hepatic steatosis, and insulin resistance were ameliorated in the treated mice. In addition, MH significantly lowered plasma triglyceride, cholesterol levels, reduced alanine transaminase (ALT), liver weight, and hepatic triglyceride level, and also ameliorated hepatic steatosis. In comparison, the *Magnolia* extract only significantly reduced ALT and hepatic triglyceride level. MH prevented cardiac hypertrophy in male obese mice via suppression of lipid accumulation, oxidative stress, and inflammation (Zhang *et al.*, 2014b). In addition, MH prevented cardiac pathogenesis and attenuated cardiac insulin signaling impairment in these obese mice (Zhang *et al.*, 2015).

#### Hair growth promotion

At a dose of 30 nM and applied for 14 days, MH significantly increased hair growth in rat vibrissa follicles by 2.5 times that of the control group (Kim *et al.*, 2011). MH promoted hair growth via the downregulation of transforming growth factors and the proliferation of dermal papilla cells. In immortalized human keratinocyte HaCaT cells, the hair-growing mechanisms of MH may involve the modulation of cell cycle arrest and ROS production (Kang *et al.*, 2011) and the suppression of cell growth

**Table 1.** Other bioactivities of 4-*O*-methylhonokiol from *Magnolia* species.

Bioactivity	Effect and mechanism of 4- <i>O</i> -methylhonokiol (reference)
Antiseizure	Possessed significant antiseizure activity using the EKP zebrafish model (Li <i>et al.</i> , 2020).
Neuroprotection	Induced neurite outgrowth in rat embryonic neuronal cells via increase in neurotrophic factor levels and ERK activation (Lee <i>et al.</i> , 2009b).
PPAR modulation	Exhibited significant competitive binding activities against PPAR $\alpha$ and PPAR $\gamma$ (Han <i>et al.</i> , 2020).
Inhibition of OCG	Inhibited OCG in RAW264.7 cells and in primary human macrophages by being an active inverse agonist of CB2 receptors (Schuehly <i>et al.</i> , 2011).
Protection against liver damage	Suppressed RANKL-induced OCG in macrophages derived from the bone marrow (Park <i>et al.</i> , 2017).
Protection against liver damage	Exerted hepatoprotection in alcohol-induced liver damage by inducing MMPs, NAEs, and AEA and by preventing activation of HSC (Patsenker <i>et al.</i> , 2017).
Treatment of cannabis dependence	Could be used to treat cannabis-induced withdrawal and craving in the treatment of cannabis dependence (Coppola and Mondola, 2014).
Alleviation of BBB dysfunction	Enhanced RSA in lipid and hydrophobic environments, crucial for the physiological activity of the BBB (Han <i>et al.</i> , 2015).
Amelioration of CD	Stabilized cognitive function in double transgenic mice by significantly reducing the deficit in learning and memory (Jung <i>et al.</i> , 2014).

via the inhibition of both canonical and noncanonical pathways (Kim *et al.*, 2017).

### Influence on embryo anomalies

Studies have shown that MH has influence on teratogenesis or embryo anomalies. In cultured mouse embryos, MH inhibited nicotine-induced teratogenesis. Reduction in anomalies of the cultured embryos was attributed to modulation of apoptosis, oxidative stress, and inflammation (Lin *et al.*, 2014; Yon *et al.*, 2013). Results suggested that MH can be developed into a protective agent against teratogenesis caused by maternal smoking during pregnancy. However, another study showed that MH was found to cause adverse changes in the cells and morphology of medaka embryos, characterized by inflammation, thrombosis, and spinal and cardiac deformities (Singha *et al.*, 2019).

### Other properties

Other pharmacological properties of MH include inhibition of antiseizure, neuroprotection, osteoclastogenesis, protection against liver injury, treatment of cannabis dependence, alleviation of blood–brain barrier dysfunction, amelioration of cognitive dysfunction, and reception of cannabinoid 2 (Table 1).

Abbreviations: AEA = anandamide, BBB = blood-brain barrier, CB2 = cannabinoid type 2, CD = cognitive dysfunction, EKP = ethylketopentenoate, ERK = extracellular signal-regulated kinases, HSC = hepatic stellate cells, MMP = matrix metalloproteinases, NAEs = N-acetyethanolamines, OCG = osteoclastogenesis, PPAR = peroxisome proliferator-activated receptor, RANKL = receptor activator of NF- $\kappa$ B ligand, and RSA = radical scavenging activity.

### CONCLUSION

From *Magnolia*, neolignans such as honokiol and magnolol are well studied. MH is lesser known and has tremendous prospects for new and further research. Further studies warranted are the cellular and molecular mechanisms underlying the effects of MH on various types of cancer and on neurodegenerative diseases, notably AD. Some research needs to be repeated as the results are either questionable or conflicting. MH has been reported to exert anticancer properties towards cervical, colon, lung, oral, and prostate cancer cells. Studies that yielded negative results using other cancer cell lines should also be published. The neuropharmacological benefits of MH in the prevention and/or treatment of neuroinflammation, anxiety, memory impairment, and cognitive dysfunction present promising research opportunities. Structure–activity relationship studies of MH are lacking. Finally, opportunities for multidisciplinary research exist whereby scientists in natural products chemistry, biochemistry, and pharmacology can work together to produce more in-depth and meaningful results. Finally, the perspectives of MH have the potential for development into agents for reducing or overcoming anxiety, multidrug resistance of cancer cells, teratogenesis caused by maternal smoking during pregnancy, memory deficiencies, and neuroinflammation.

### CONFLICT OF INTEREST

The author has no funding or any other conflict of interest in this work.

### AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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This study does not involve experiments on animals or human subjects.

### DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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